FORMULATION AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF ZANAMIVIR USING DIFFERENT POLYMERS

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LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS AND UNITS

GI	Gastro Intestinal
GRT	Gastric Retention Time
GET	Gastric Emptying Time
GRDF	Gastro Retentive Dosage Form
%	Percentage
MMC	Migrating Myoelectric Complex
FDDS	Floating Drug Delivery System
g/cm^3	gram / centimeter
mm	Millimeter
HCl	Hydrocloric Acid
Mcg	Microgram
PVP	Poly Vinyl Pyrrolidine
HPMC	Hydroxy Propyl Methyl Cellulose
SEMC	Sodium Carboxy Methyl Cellulose
MCC	Micro Crystalline Cellulose
CI	Carr's Index
Kg	Kilogram

BP	British Pharmacopia
EP	Europian Pharmacopia
USP	United States Pharmacopia
FTIR	Fourier Transform Infra Red Spectracopy
BD	Bulk Density
TD	Tapped Density
RH	Relative Humidity
ICH	International Council Hormanisation
$t^{½}$	Half Life
TFT	Total Floating Time
FLT	Floating Log Time

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1. INTRODUCTION

1.1. Oral Controlled Release Drug Delivery Systems[1, 2]:

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are[3, 4]: -

1) Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to

the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

1.2. SCOPE OF THE STUDY:

Conventional oral controlled dosage forms suffer from mainly two adversities. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. Altering the gastric emptying can overcome these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.

Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs.

i. That are locally active in stomach,

ii. That have an absorption window in the stomach or in the upper small intestine,

iii. That are unstable in the intestinal or colonic environment,

iv. Have low solubility at high pH values.

1.3. Gastro retentive Dosage Form (GRDF) [5, 6]:

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as –

1) This application is especially effective in sparingly soluble and insoluble drugs, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub mucosal tissue of stomach)

3) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents are taken up only from very specific sites of the GI mucosa.

1.3.1. PHYSIOLOGY OF GASTRO INTESTINAL TRACT:

Physiology of gastro intestinal tract

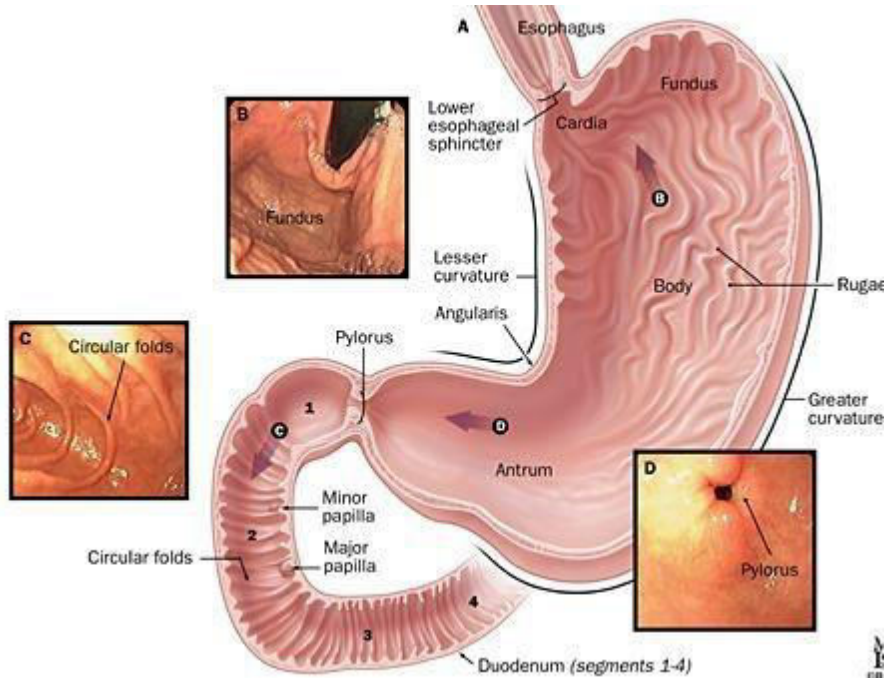


Fig.No:1. Diagram of Stomach

1.3.2. Factors Controlling Gastric Retention Time of Dosage Form[6, 7]:the gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.

- **Density of dosage form**: – the density of gastric fluid is reported to be 1.004g/cm^3.The density of the dosage form should be less than this for buoyancy, so that it is retained in stomach for longer period of time. The dosage form may be having a high density in the beginning, but due to reduction in density by swelling it will float in stomach.

- **Size of the dosage from**: –studies on the effect of particle size on gastric retention have been inconclusive. The non-disintegrating tablets as large as 7mm can be emptied from human stomach during the post-prandial period, while 13mm tablets are retained until arrival of subsequent sweeping "housekeeper wave". This emphasizes the need for size enlargement of DF in stomach in order to prolong GRT.

- **Shape of dosage form** – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KPSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.

- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release

profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

- **Caloric content** – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

- **Gender** – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.

- **Posture** – GRT can vary between supine and upright ambulatory states of the patient. Concomitant drug administration – Anticholinergics like Atropine and Propantheline, opiates like Codeine and prokinetic agents like Metoclopramide and Cisapride.

BIOLOGICAL ASPECTS OF GRDFs:

Role of GI tract[34]:

Stomach

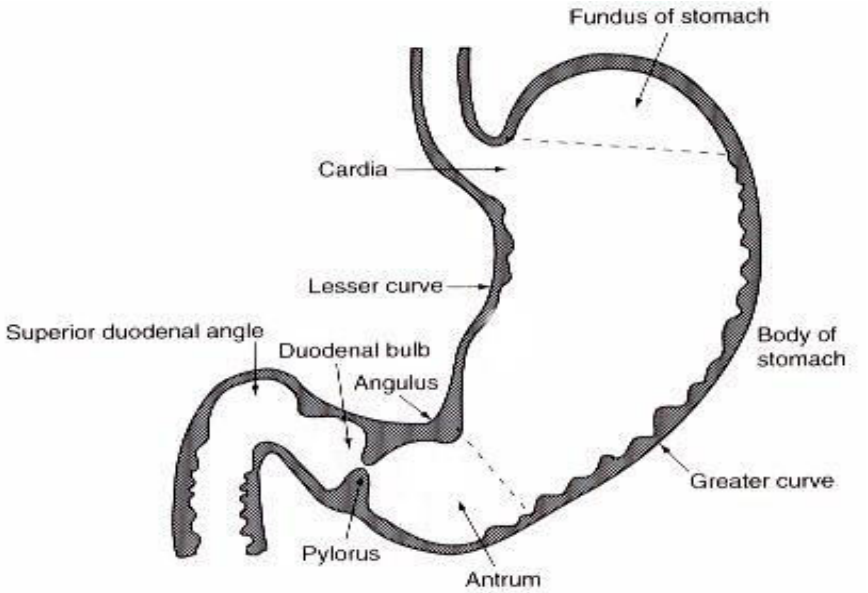


Fig.No:2.Anatomy of Stomach

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

The stomach is divided into three anatomical regions. I) Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. The digestive mode and interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as interdigestive my electric cycle.

Phase I	:	Period of no contraction.
Phase II	:	Period of intermittent contraction.
Phase III	:	Period of regular contractions at the maximal frequency that migrate distally.

Phase IV : Is the transition period of 0-5 mins between Phase III & I.

Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle[14, 15].

APPROACHES TO GASTRIC RETENTION[35]

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Floating systems, Bio adhesive systems, swelling and expanding systems, High density systems, Modified systems

Buoyant/ Floating Systems:

Floating Drug Delivery System (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug

concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

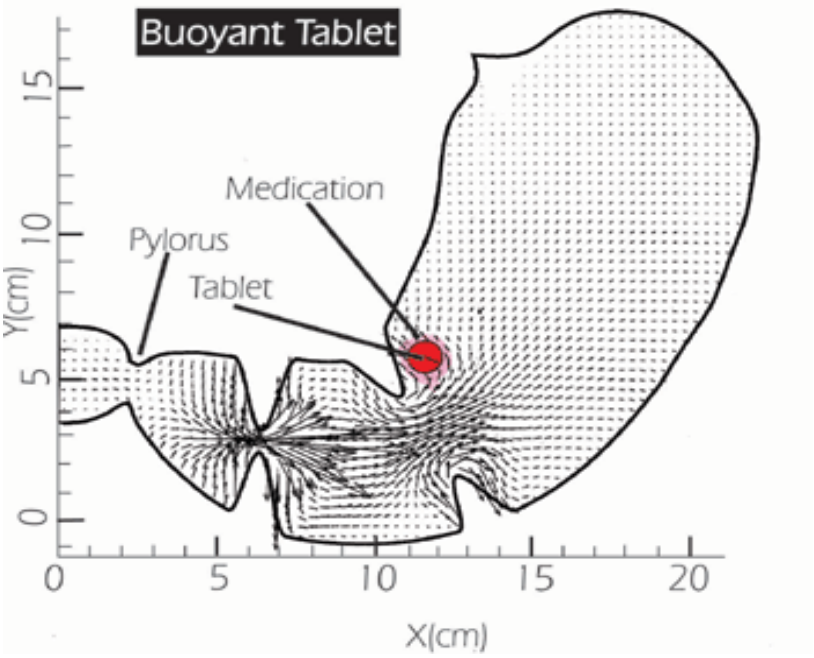


Fig.No:3.Graphic of Buoyant tablet, which is less dense than the stomach fluid and therefore remains in the fundus.

Bio/Muco-adhesive Systems:

Bio/Muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers.

The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three broad categories: –

1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.
3. Receptor-mediated adhesion.

Swelling and Expanding Systems:

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type system", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

High Density Systems: [35]

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Fig. 4.

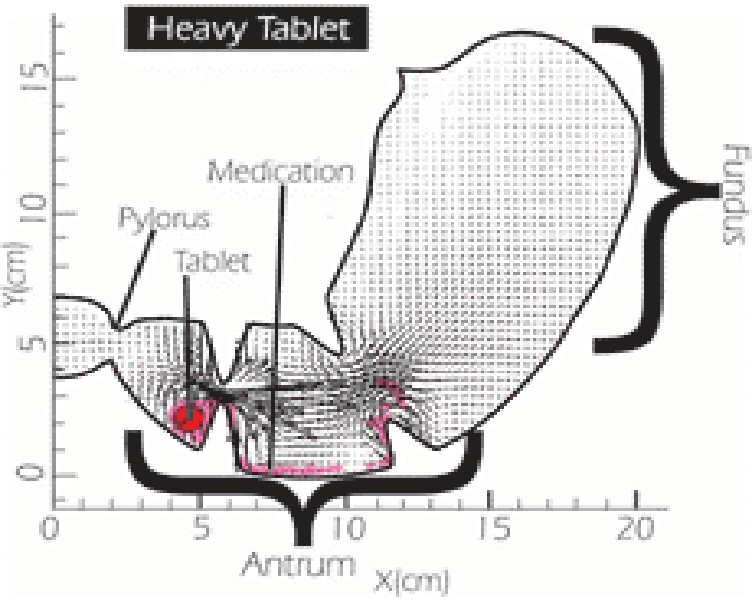


Fig.No:4. Graphic of heavy tablet, which is denser than the stomach fluid and therefore sinks to the antrum.

Incorporation of Passage Delaying Food Agents:

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying

after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}

Ion Exchange Resins:

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic Regulated Systems:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio erodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

1.4.FLOATING DRUG DELIVERY SYSTEMS (FDDS)

1.4.1. Advantages of FDDS[25, 26]:

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.

2. Controlled delivery of drugs.

3. Delivery of drugs for local action in the stomach.

4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.

5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.

6. Simple and conventional equipment for manufacture.

7. Ease of administration and better patient compliance.

8. Site-specific drug delivery.

1.4.2. Disadvantages of FDDS:

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametric size. Therefore patients should not be dosed with floating forms just before going to bed.

Floatable Drug Delivery Systems [8]:

Table.No:1. Lists of Drugs

S. No.	DOSAGE FORM	DRUGS
1	Microspheres	Aspirin, Griseofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
2	Granules	Diclofenac sodium, Indomethacin, Predmisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid.
6	Tablets/pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnazirine, Diltiazem, Fluorouracil,

Table.No:2. Marketed Products of FDDS

S. NO.	Brand Name	Drug (Dose)	Company, Country	Remarks
1.	Modapar	Levodopa(100mg), Benserazide(25 mg)	HRoche Products, USA	Floating CR capsule
2.	Valrelease	Diazepam (15 mg)	Hoffmann-LaRocheUSA	Floating capsule
3.	Liquid Gavison	Al hydroxide (95 mg),	GlaxoSmith Kline, India	Effervescent floating liquid alginate
4.	Topalkan	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD	Ciprofloxacin(1gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec	Misoprostal(10mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

1.4.3.TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS) [36]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and

B. Non- Effervescent System.

EFFERVESCENT SYSTEM:-

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems.

Gas – Generating Systems:

Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS):

These are as shown in Fig.5 and formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

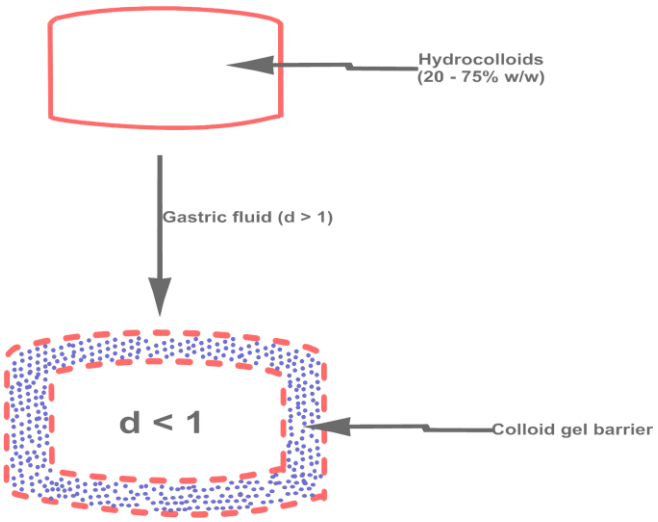


Fig.No: 5. Intra Gastric Single Layer Buoyant Tablet.

Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Fig 6 and containing two layers i.e,

i. Immediate release layer and

ii. Sustained release layer.

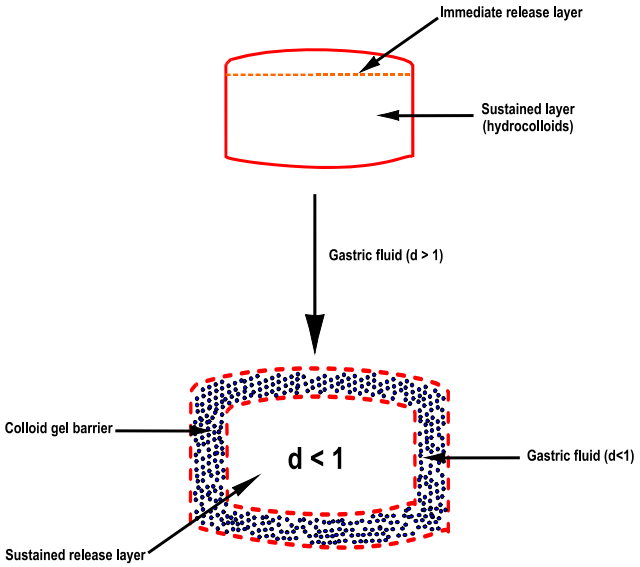


Fig.No:6. Intra Gastric Bilayer Buoyant Tablet.

Multiple Unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layers consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

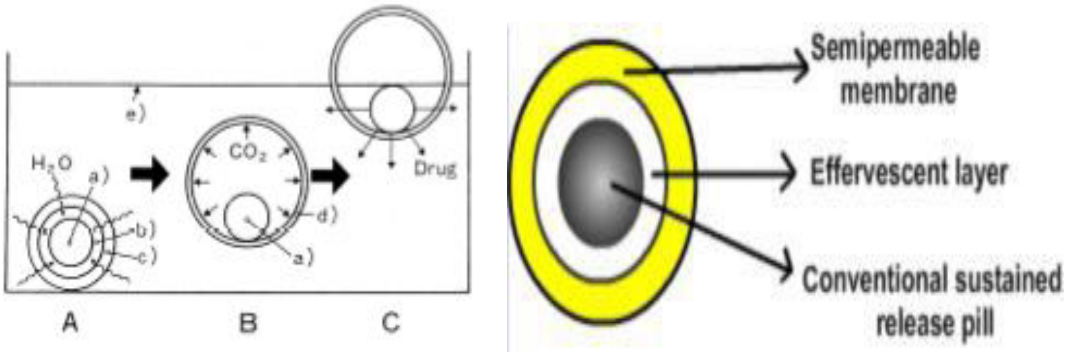


Fig.No:7. A multi-unit oral buoyant dosage system. Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug.

Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C)

Volatile Liquid / Vacuum Containing Systems:[23]

Intragastric Floating Gastrointestinal Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment, as shown in Fig 8.

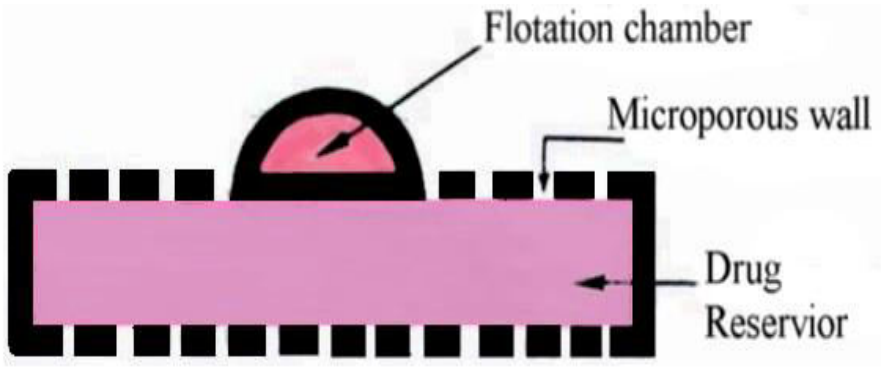


Fig.No:8. Intra Gastric Floating Gastrointestinal Drug Delivery Device

Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule.

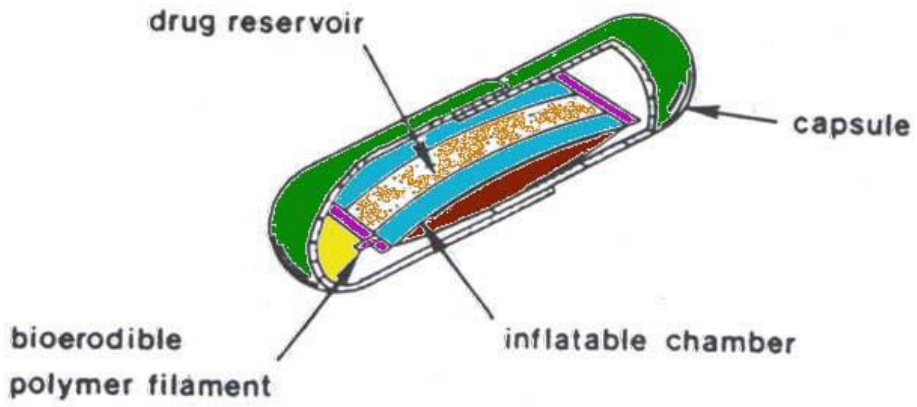


Fig.No:9. Inflatable Gastrointestinal Delivery System

After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig 9.

Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig10.

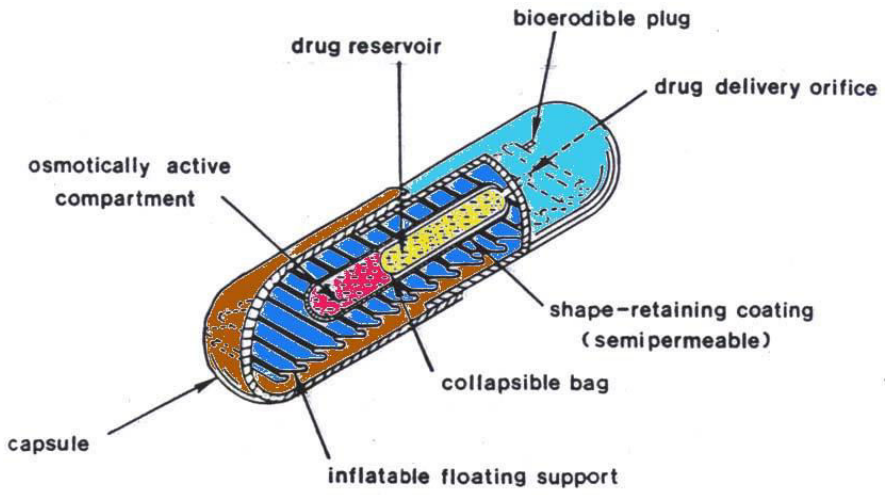


Fig.No:10. Intragastric Osmotically Controlled Drug Delivery System

NON-EFFERVESCENT SYSTEMS: [23]

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. The various types of this system are as:

Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Bilayer Floating Tablets:

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

Alginate Beads:

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours.

Hollow Microspheres:

Hollow microspheres (micro balloons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The micro balloons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in-vitro*.

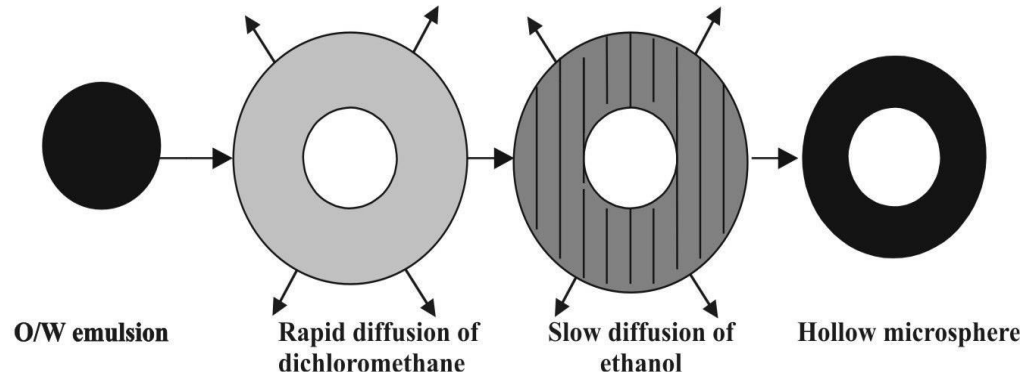


Fig.No:11. Hallow microspheres

2. LITERATURE REVIEW

Narendra, *et.al.,* [9] reported optimization of bilayer floating tablet containing Nevirapine as a model drug for gastric retention. They employed a 23 factorial design in formulating the GFDDS with total polymer content-to-drug ratio (X1), polymer-to-polymer ratio (X2), and different viscosity grades of HPMC (X3) as independent variables. The results indicate that X1 andX2 -significantly affected the floating time and release properties but the effect of different viscosity grades of HPMC (K4M and K10M) was non-significant.

Srivastava, *et.al.,* [10] prepared floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. The tablets were prepared by direct compression technique, using polymers such as HPMC K15M, K4M, Guar gum (GG), and sodium carboxy methylcellulose (SCMC), alone or in combination and other standard excipients. The effect of effervescent on buoyancy and drug release pattern was also studied. *In-vitro* release mechanism was evaluated by linear regression analysis. GG- and SCMC-based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles.

Dave, *et.al.,* [11] reported a gastro retentive drug delivery system of ranitidine hydrochloride. Guar gum, Xanthan gum, and hydroxyl propyl methylcellulose were evaluated for gel forming properties. Sodium bicarbonate was incorporated as a gas-

generating agent. They investigated the effect of citric acid and stearic acid on drug release profile and floating properties. They concluded that the proper balance between a release rate retardant and a release rate enhancer could produce a drug dissolution profile similar to a theoretical dissolution profile.

Dalavi.V.V., *et.al.,*[12] developed a Gastro retentive tablet of Zidovudine to enhance its bioavailability and sustained action. Zidovudine is a novel compound used in the treatment of HIV. In 32 factorial designs, amount of HPMC K4M (X1) and gas generating agents (X2) were selected as independent variable. The time required for 50% drug release t50% (Y1) was selected as dependent variable. The results of factorial design showed that factor X1 and X2 significantly affect the studied dependent variables. The formulation with good floating time (24hrs) and the percent drug release (98.05) emerged as optimal.

Sivabalan.M., *et.al.,*[13] Formulated and evaluated hydro dynamically balanced controlled drug delivery system of Glipizide. The formula selected for design had a combination of Glipizide, HPMC, EC and MC. The tablets were prepared by direct compression method and evaluated for Glipizide content, *in-vitro* release profile and buoyancy. The buoyancy of the tablets was ranged between 10.917±0.4403hrs and 16.237±0.1217 hrs, the maximum buoyancy was seen in G8, which has a high level of drug to polymer ratio. The *in-vitro* release was found to be in the range of 59.25% to 79.50%. The Glipizide content in the formulation varied between 91–100%. The

formulation G8 has an *in-vitro* release of 59.25, showed the release of the drug in the controlled manner.

***Sunil K. Jain, et.al.,*[14]** Prepared floating microspheres consisting of (1) calcium silicate as porous carrier; (2) orlistat, an oral anti-obesity agent; and (3) Eudragit S as polymer, by solvent evaporation method and to evaluate their gastro-retentive and controlled-release properties. The effect of various formulation and process variables on the particle morphology, micromeritic properties, *in-vitro* floating behavior, percentage drug entrapment, and *in-vitro* drug release was studied. The microspheres were found to be regular in shape and highly porous. Microsphere formulation CS4, containing 200 mg calcium silicate, showed the best floating ability (88% ± 4% buoyancy) in simulated gastric fluid as compared with other formulations. Release pattern of orlistat in simulated gastric fluid from all floating microspheres followed Higuchi matrix model and Korsmeyer-Peppas model. The enhanced elimination half-life observed after pharmacokinetic investigations in the present study is due to the floating nature of the designed formulations.

S. B. Bhise, *et.al.,*[15] studied sustained release floating capsules for theophylline was fabricated using drug: polymer ratio of 30:70. The hydrocolloids were used in different proportions and four formulations were prepared. These formulations were optimized on the basis of buoyancy, matrix integrity, duration of floating and *in-vitro* drug release. All the four formulations showed good buoyancy and matrix integrity. The duration of floating was more than 12 h for all formulations.

In-vitro drug release study of these formulations indicated controlled release of theophylline and about 76 percent drug was released at the end of 12 h.

Vishal G. Karkhile, *et.al.,*[16] Floating tablet of Furosemide (FUR) was prepared by direct compression technique. Furosemide was chosen as model drug because it is slightly soluble in water and poorly absorb from lower intestine. PEG-6000 is used as carrier agent for increasing solubility of Furosemide in water. Hydroxypropylmethylcellulose, sodium bicarbonate and carbopol were used as matrixing agent, gas generating agent and floating agent respectively. The tablets were evaluated for *in-vitro* buoyancy and dissolution studies. Tablets were evaluated for physical characteristics. The data of *in-vitro* dissolution study of prepared floating tablet formulation showed zero order plots which was found to be fairly linear as indicated by its high regression value (R^2=0.9772 to 0.9911). The optimized floating tablet batch (F3) shows drug release in a controlled manner with higher dissolution for 12 hr.

Patel, *et.al.,*[17] prepared a floating drug delivery system of famotidine. Famotidine having poor absorption in acidic environment (upper GIT). When given orally, it shows the bioavailability near to 50%. To overcome these drawbacks, the present study was undertaken to investigate the floating dosage form of famotidine. Floating tablets were prepared using Direct Compression. Six formulations were prepared containing gel-forming agent (HPMC K4M) and retardant (Na-CMC) in different ratio and it was found that gas generating agent (NaHCO3) reacts with HCl

and liberates CO2 which creates pores in tablet and elevates swelling and maintains buoyancy. The prepared tablets were evaluated for content uniformity, hardness, friability, buoyancy, swelling index and *in-vitro* dissolution studies. Further selected formulation was subjected for short term stability studies for one and two month at temperature of 25°c and 40°c respectively.

Chander Shekar, *et.al.,*[18] Prepared a gastro retentive drug delivery system of Ketoconazole by direct compression technology. HPMC K100LV, HPMC K15M, Ethyl Cellulose and effervescent sodium bicarbonate formed the floating tablet. The prepared tablets exhibited satisfactory physico-chemical characteristics. Final formulation released approximately 89.21% drug in 24 h *in-vitro*, while the floating lag time was not more than 35 Sec and the tablet remained floatable throughout all studies. The tablets with HPMCK15M were found to float for longer duration as compared with formulations containing HPMCK 4 M. The release of Ketoconazole was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The optimized formulation was found to be buoyant for 24 hr in stomach. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Pramod Patil, *et.al.,*[19] developed floating tablets of ofloxacin which were designed to prolong the gastric residence time after oral administration. Ofloxacin floating tablets were prepared by wet granulation method incorporating natural polymer like guar gum, locust bean gum, either alone or in combination with HPMC

K100M as swelling polymers, with sodium bicarbonate as gas generating agent and were evaluated for physico-chemical parameters. All the formulation showed compliance with pharmacopeia standards. Based on the evaluation results, F3 and F6 formulations were selected as the best formulations and were checked for stability as per ICH guidelines. These results indicated that the selected formulations were stable. The drug release of optimized formulation follows theHiguchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppasequation.

Tarique khan, *et.al.,*[20] studied development and *in-vitro* evaluation of the floating matrix tablets, which after oral administration can prolong the gastric residence time, increase the drug bioavailability. A polymer (sodium carboxy methyl cellulose or hydroxyl propyl methylcellulose K4M, K15M) was added to control the drug release. The time to flotation could be controlled by the composition (type of filler, concentration of effervescent agents) and hardness of the tablet. Six different formulations were prepared i.e. D1, D2, D3, D4, D5, and D6 by varying the polymers ratio. All the formulations were evaluated for physico-chemical parameters. The formulation D4 shows 99% drug release at the end of 12 h *in-vitro* and floating lag time was 30 sec and tablet remained buoyant throughout studies.

Thakkar, *et.al.,*[21] Formulated and evaluated the levofloxacin hemihydrates floating tablets that were prepared by direct compression method using gelucire 43/01 and HPMC polymers in different ratio. The *in-vitro* release study revealed the fact

that the release rate of drug was decreased by increasing the proportions of gelucire 43/01 by 5 to 40% matrix tablets containing 25% HPMCK4M and 15% gelucire 43/01.

Bomma, *et.al.,*[22] Prepared floating matrix tablets of norfloxacin which were developed to prolong gastric residence time leading to an increase in drug bioavailability by using wet granulation technique using polymers such as HPMCK4M, HPMCK100M and Xanthan gum. The tablets exhibited controlled and prolonged drug release profile while floating over dissolution medium was confirmed as drug release mechanism from these tablets.

Rahman, *et.al.,*[23] Developed a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC-K15Mgrade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934P, alone or in combination with the drug. Final formulation released approximately 95% drug in 24 h *in-vitro*, while the floating lag time was 10 min and the tablet remained floatable throughout all studies. Final formulation followed the higuchi release model and showed no significant change in physical appearance, drug content, floatability or *in-vitro* dissolution pattern after storage at 45 °C/75% RH for three months.

Amin, *et.al.,*[24] developed a gastro retentive drug delivery system of ranitidine hydrochloride which was designed using guar gum, xanthan gum and HPMC. Sodium

bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 3^2 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine HCl from a gastro retentive formulation.

Li, *et.al.,*[25] Formulated using 2x3 full factorial designs for calcium delivery. HPMC was used as a low-density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system. High-viscosity polymers had good effect on floating properties. The residual floating force values of the different grades of HPMC were in the order K4 M~ E4 M~K100 LV> E5 LV but different polymers with same viscosity, i.e., HPMC K4M, HPMC E4M did not show any significant effect on floating property. Better floating was achieved at a higher HPMC/Carbopol ratio and this result demonstrated that Carbopol has a negative effect on the floating behavior.

J.Sahoo, *et.al.,*[26] Studied the release of Propranolol hydrochloride from matrix tablets with hydroxy propyl methyl cellulose (HPMC K15M) or Kollidon®SR at different concentrations was investigated with a view to developing twice daily sustained release dosage form using direct compression technique. The resulting

matrix tablets prepared with HPMC K15M or Kollidon®SR fulfilled all the official requirements of tablet dosage forms. Formulations were evaluated for the release of Propranolol hydrochloride over a period of 12 h in pH 6.8 phosphate buffer using USP type II dissolution apparatus. Propranolol hydrochloride and pure Kollidon®SR or HPMC K15M compatibility interactions was investigated by using FTIR spectroscopy and DSC and, these studies revealed that there was no well defined chemical interaction between Propranolol hydrochloride with Kollidon®SR or HPMC K15M. Tablets were exposed to 40 °C/75% of RH in open disc for stability. The *in-vitro* drug release study revealed that HPMC K15 at a concentration of 40% of the dosage form weight was able to control the release of Propranolol hydrochloride for 12 h, exhibit non-Fickian diffusion with first-order release kinetics where as at 40% Kollidon®SR same dosage forms show zero-order release kinetics.

Narasaiah, *et.al.,*[27] prepared a gastro-retentive drug delivery system of Sumatriptan Succinate as a model drug. The floating tablets were prepared by wet granulation method using hydroxy propyl methylcellulose (HPMC) as gel-forming agent. Sodium bicarbonate and citric acid were incorporated as gas-generating agents. The tablets were physically characterized and evaluated for *in-vitro* release characteristics for 8 hrs in 0.1N HCl at 37°C. The physical characterization of the tablets was found within the limits. By comparing dissolution profiles, the formulation F5 was considered as a better formulation. The drug release for all the formulations were followed by zero order kinetics and Peppas modeling. The

diffusion exponent of formulations was found (n<0.89) to be non-fickian (Anomalous) diffusion mechanism.

AJ.Shinde, *et.al.,*[28] prepared a gastro retentive floating drug delivery system (GFDDS) of cephalexin (CFL) employing the hydrophilic polymer hydroxy propyl methylcellulose (HPMC), gas generating agent sodium bicarbonate and citric acid. A 32 factorial design was applied systematically; the amount of citric acid (X1) and amount of HPMC K100M (X2) were selected as independent variables. The time required for 50% drug release (t50%), percentage drug release at 12 hours (Q12) and percentage drug release at 6 hours (Q6) were selected as dependent variables. The results of factorial design indicated that high level of HPMC K100M and citric acid favors preparation of floating sustained release tablet of cephalexin. The granules were prepared by wet granulation method and evaluated for their granules properties. Tablets were compressed by Mini press rotary tablet machine and evaluated with different parameters like diameter, thickness, average weight, hardness, friability, drug content, *in-vitro* buoyancy study, swelling characteristics, scanning electron microscopy, and kinetic release data. The tablets containing CFL released 72.28 to 99.461 % of drug at the end of 12 hrs by *in-vitro* release study. The drug release from the tablets was sufficiently sustained followed the Korsmeyer-Peppas model controlled mechanism of cephalexin tablet.

3. AIM AND OBJECTIVE

The present work is aimed to formulate Zanamivir floating tablets using different hydrophilic and hydrophobic polymers like HPMC, Ethyl cellulose, Xanthum gum, guar gum and gas generating agent Sodium bicarbonate.

The objective of the present work is to develop Gastro retensive dosage form that could retain the anti- viral agent namely Zanamivir in the stomach for longer periods of time delivering the drug to the site of action, i.e., stomach.

Zanamivir is an anti-viral agent. It is soluble in water with 75% bioavailability. HPMC is used as a swelling agent, Guar gum and Xanthum gum is used as binding agent. Ethyl cellulose is used as matrix form agent. PVP is used as a suspending agent. sodium bicarbonate is used as a gas forming agent. MCC is used as a disinter grant and diluent. Magnesium stearate is used as a lubricant.

The prepared Zanamivir tablets will be evaluated for drug content, entrapment efficiency, particle size analysis, post compression studies, *In-vitro* buoyancy studies, swelling index studies, *in-vitro* dissolution studies, release kinetics, stability studies.

4. PLAN OF THE WORK

The plan of work was given below

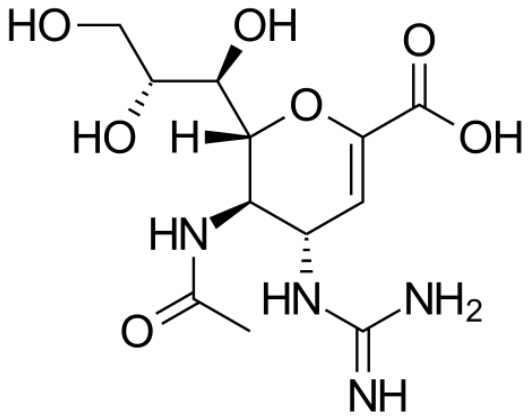
- Preformulation studies.
    1. Identification of drug
    2. Drug – Excipients compatibility studies by FTIR spectrophotometry
    3. Pre compression studies
- Formulation of floating tablets of Zanamivir.
- Evaluation studies
    - Post compression studies
    - Drug content
    - *In-vitro* buoyancy studies
    - Swelling index studies
    - *In-vitro* dissolution studies
- Release kinetics
- Stability studies

5. DRUG AND POLYMER PROFILES

5.1. DRUG PROFILE

ZANAMIVIR

Description : An acetamido cyclohexene that is a structural homolog of sialic acid and inhibits neuraminidase.



Structure Formula :

Synonyms : Zanamivir phosphate

Categories : Antiviral Agents

Enzyme Inhibitors

Weight:Average:332.31

Chemical Formula : $C_{12}H_{20}N_4O_7$

IUPAC Name : (2*R*,3*R*,4*S*)-4-guanidino-3-(prop-1-en-2-ylamino)-2-((1*R*,2*R*)-1,2,3-trihydroxypropyl)-3,4-dihydro-2*H*-pyran-6-carboxylic acid

TAXONOMY

Kingdom : Organic

Classes : Carboxylic Acids and Derivatives

Cyclohexenes and Derivatives

Carboxylic Acids and Derivatives

Alkanes and Alkenes

Acetates

Substructure : Amino Ketones

Aliphatic and Aryl Amines

Ethers

Carboxamides and Derivatives

Cyclohexenes and Derivatives

PHARMACOLOGY

Indication : Zanamivir (Relenza) is for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days. It is also used for the prophylaxis of influenza in adult patients and adolescents 13 years and older

Pharmacodynamics : Zanamivir is an antiviral drug, a neuraminidase inhibitor used in the treatment and prophylaxis of both influenza A and influenza B. Zanamivir is a prodrug (usually administered as phosphate), it is hydrolysed hepatically to the active metabolite, the free carboxylate of zanamivir (GS4071). Like zanamivir, zanamivir acts as a transition-state analogue inhibitor of influenza neuraminidase.

Mechanism of action : Zanamivir is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, zanamivir carboxylate. The proposed mechanism of action of zanamivir is inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Absorption : Readily absorbed from the gastrointestinal tract after oral administration with a bioavailability of 75%.

Volume of distribution : 23 to 26 L

Protein binding : Zanamivir carboxylate: low (3%), Zanamivir free base: 42%.

Metabolism : Extensively converted to zanamivir carboxylate by esterases located predominantly in the liver. Neither zanamivir nor zanamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms. At least 75% of an oral dose reaches the systemic circulation as zanamivir carboxylate.

Route of elimination : Absorbed zanamivir is primarily (>90%) eliminated by conversion to zanamivir carboxylate. Zanamivir carboxylate is not further metabolized and is eliminated in the urine. Zanamivir carboxylate is eliminated entirely (>99%) by renal excretion.

Half life : 1 to 3 hours in most subjects after oral administration.

Clearance : Not Available

Toxicity : At present, there has been no experience with overdose. Single doses of up to 1000 mg of zanamivir have been associated with nausea and/or vomiting. Mean LD (intravenous, mouse) = 100 mg/kg.

Affected organisms : Influenza Virus

5.2. POLYMER PROFILE

5.2.1.HYDROXY PROPYL METHYL CELLULOSE

Non-proprietary names: Bp: Hypromellose

USP: Hydroxy propyl methyl cellulose

Synonyms: Methyl hydroxy propyl cellulose, propylene glycol either of methylcellulose, methylcellulose, methylcellulose propylene glycol ether.

Chemical name:

Cellulose, 2-hydroxypropyl-methyl ether

Empirical formula:

C8H15O6 – (C10H18O6) n – C8H15O5

Description: It occurs as odorless and tasteless creamy white colored fibrous or glandular powder.

FUNCTIONAL CATEGORY: Coating agent, film former, tablet binder, stabilizing agent, suspending agent, viscosity increasing agent.

Density: 0.25 – 0.70 g/cm3

Solubility: Soluble in cold water forming viscous colloidal solution, insoluble in chloroform, ethanol and ether, but soluble in mixtures of ethanol and methylene chloride.

Viscosity: HPMC K4M; HPMCK15M. HPMC K100M;

Stability and storage: It is stable although it is slightly hygroscopic. The bulk material should be stored in airtight container in a cold and dry place. Increase in temperature reduces the viscosity of the solution.

Safety: It is widely used in many oral and topical pharmaceutical formulations. It is generally regarded as a non-toxic and non-irritant material, although excessive consumption may have laxative effect**.**

Pharmaceutical Applications:

1. Film-former in tablet film coating: Lower viscosity grades are used in aqueous film coating and higher viscosity grades are used in solvent film coating.

2. Binder in tablet granulations: 2.5% high-viscosity grades are used to retard the release of water-soluble drugs.

3. As a Thickening agent: Thickening agent added to vehicles for eye drops & artificial fear solutions at 0.45 - 1.0% concentrations.

4. As a protective colloid: Prevents droplets and particles from Coalescing or agglomerating, thus inhibiting the formation of sediments. It is used as emulsifier, suspending agent & stabilizer in gels & ointments. As an adhesive in plastic bandages.

5.2.2. SODIUM BICARBONATE

Non-proprietary names: BP/EP: sodium bicarbonate

Synonym: Baking soda, e-500, and monosodium carbonate.

Chemical name: carbonic acid, monosodium salt, monosodium carbonate.

Empirical formula: NaHCO3

Molecular weight: 84.01

Category: alkalizing agent, therapeutic agent.

Description: it is an odorless, white crystalline powder with slight alkaline taste.

Acidity/ alkalinity: pH 8.3 for freshly prepared 0.1m aqueous solution at 250c.

Density: 2.159 g/cm3

Solubility: Soluble in water, practically insoluble in ethanol.

Stability and storage: Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in well-closed container in a cool dry place.

Safety: Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

Applications:

1. Employed as a source of carbon dioxide in effervescent tablets and granules.
2. Also used to buffer the drug molecules that are weak acids.
3. Used in solutions as buffering agent.
4. Also used as freeze-drying stabilizer.
5. As a gas forming agent.

5.2.3.MICROCRYSTALLINE CELLULOSE

Empirical formula: ($C_6H_{10}O_5$)

Molecular weight: n~220

Category: Adsorbent; suspending agent, tablet and capsule diluents, tablet disintegrate.

Description: Itoccurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Density (true): 1.512-1.668 g/cm^3

Solubility: Slightly soluble in 5% W/V sodium hydroxide solution

Application in pharmaceutical Formulation Technology

1. Microcrystalline cellulose is widely used in pharmaceuticals primarily as binder/diluents in oral tablet and capsule formulations.

2. Microcrystalline cellulose also has some lubricant and disintegrates properties that make it useful in tabulating.

Table.No:3.Use of MCC

Use	Concentration (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule binder/ diluent	20-90
Tablet disintegrate	5-15
Tablet binder/ diluent	20-90

Safety: Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may, however, have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulation

5.2.4.MAGNESIUM STEARATE

Synonyms: Stearic acid magnesium salt,

Magnesium octa decanoate

Chemical name: Octdecanoic acid magnesium salt

Nonproprietary names: BP- Magnesium stearate

PHEUR-Magnesia stearate

USP NF - magnesium stearate.

Description: Magnesium stearate is a fine, white, precipitated, milled, impalpable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to touch and readily adheres to skin.

Applications:

1. Magnesium stearate is widely used in cosmetics, foods and pharmaceuticals.
2. It is primarily used as lubricant in capsule and tablet manufacture at a concentration between 0.25-5.0 % concentrations.
3. As an excipient, it is mainly used as directly compressible tablet diluents.
4. Also used in micro sphere formulations.
5. Used to absorb liquids, such as flavors in tabulating process.

5.2.5.ETHYL CELLULOSE

Nonproprietary Names

BP: Ethylcellulose

PhEur: Ethylcellulose

USP-NF: Ethylcellulose

Synonyms

Aquacoat ECD;Aqualon;Ashacel; E462;Ethocel; ethylcellulosum; Surelease.

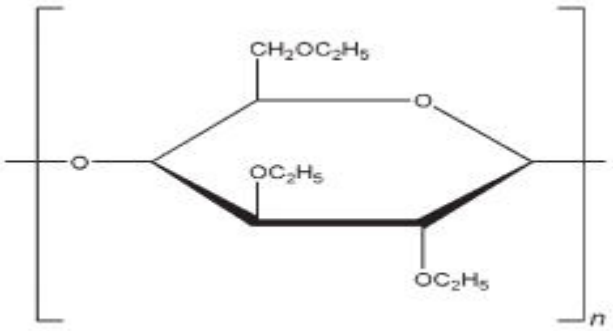
Chemical Name

Cellulose ethyl ether

Empirical Formula and Molecular Weight

Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer ofb-anhydroglucose units joined together by acetal linkages.

Structural Formula



Functional Category

Coating agent; flavoring agent; tablet binder; tablet filler; viscosityincreasing agent.

Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations.

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.

Ethylcellulose coatings are used to modify the release of a drug,to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former.

Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility,by the addition of hypromellose or a plasticizer;. An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) orSurelease(Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents. Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

High-viscosity grades of ethylcellulose are used in drug microencapsulation. Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wetgranulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances.In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is

used.Ethylcellulose has been studied as a stabilizer for emulsions.Ethylcellulose is additionally used in cosmetics and food products.

Table.No:4.Uses of ethylcellulose.

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

Description

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.

Solubility

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform,methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol,and toluene

5.2.6. POVIDONE

NonproprietaryName: Povidone

Synonyms: Kollidon; plasdone; polyvinylpyrrolidone

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula: (C_6H_9NO) n

Molecular Weight: 2500–3 000 000

Functional Category: Disintegrant; dissolution enhancer; suspending agent; tablet binder.

Description: Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidone with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K90 and higher K value povidone are manufactured by drum drying and occur as plates.

Solubility: Freely soluble in acids, chloroform, ethanol (95 %), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

Stability and Storage Conditions: Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C.

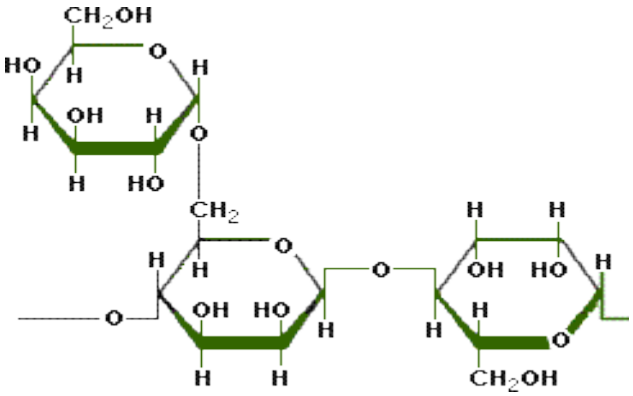
Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. As the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities: Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.

Applications: Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. It is used as a tablet binder, tablet diluent or coating agent in the concentration of 0.5-5 %. Povidone is used as a suspending and dispersing agent in the concentration of 5 %.

Related Substances: Crospovidone.

5.2.7. GUAR GUM



Nonproprietary Names:

BP, PhEur **:** Guar Galactomannan

USP-NF : Guar Gum

Synonyms **:** Galactosol, Guarflour, Jaguargum, Meyprofin.

Chemical name **:** Galactomannan polysaccharide.

Molecular Formula **:** $(C_6H_{12}O_6)n$

Molecular Weight **:** 220 000

Density **:** $1.492 g/cm^3$

Viscosity **:** 4.86 Pa s (4860 cP) for a 1% w/v dispersion.

Description : Occurs as an odorless, white to yellowish color, bland taste.

Solubility : Practically insoluble in organic solvents. In cold or hot water, disperses and swells almost immediately to forma highly viscous, thixotropic solution.

Functional category : Suspending agent, binder, disintegrator and viscosity agent.

Safety : Guar gum is widely used in foods, and oral and topical pharmaceutical formulations. Excessive consumption may cause gastrointestinal disturbance such as diarrhea ornausea[42]. It is nontoxic and nonirritant material.

Stability and storage : The aqueous guar gum dispersion has a buffering action and are stable at p^H 4-10.5. The guar gum powder should be stored in a well closed container in a cool dry place.

Pharmaceutical Applications

1. Guar gum is commonly used in cosmetics, food products and pharmaceutical formulations[43].

2. It has also been investigated in the preparation of sustained release matrix tablets[43].

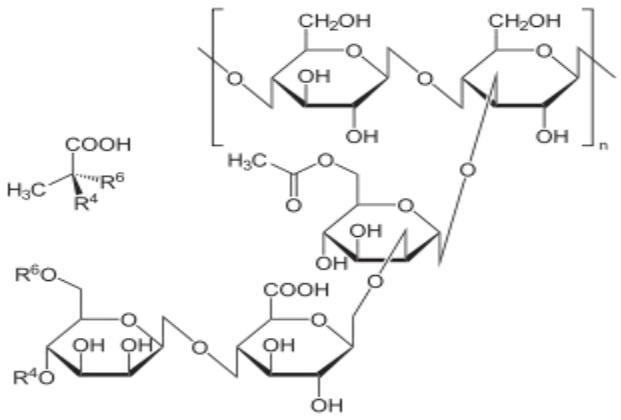
3. Guar gum is used in solid dosage forms as a binder and disintegrant.

4. It is used by suspending, thickening, and stabilizing agent.

5. Guar gum also used by controlled released carrier.

6. It has also been examined for use in colonic drug

5.2.8.XANTHAN GUM



Nonproprietary Names:

BP, USP-NF **:** Xanthan Gum

Synonyms **:** Corn sugar gum, Xanthani gummi.

Chemical Name : Xanthum Gum

Molecular Formula : $(C_{35}H_{49}O_{29})_n$

Molecular Weight : 1×10^6

Viscosity : 1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

Description : Xanthan gum occurs as a cream- or white-colored, odorless, free flowing, fine powder.

Solubility : Practically insoluble in ethanol and ether; soluble in cold or warm water.

Functional Category : Gelling agent; stabilizing agent; suspending agent; sustained- release agent; viscosity-increasing agent.

Safety : Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products, generally regarded as nontoxic and nonirritant material.

Stabilty & Storage **:** Xanthan gum is a stable material. Aqueous solutions are stable overa wide pHrange(pH 3–12), maximumstability at pH 4–10 and temperatures of 10–60°Calthough they demonstrate. The bulk material should be stored in a well-closed container in a cool, dry place.

Pharmaceutical Applications

1. It is also used as a thickening and emulsifying agent.

2. Xanthan gum has been used as a binderand in combination with Konjac glucomannanis used as an excipient for controlled colonic drug delivery.

3. Xanthan gum has also been used with guar gum for the development of a floating drug delivery system

4. Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations.

5. Xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results.

6. METHODOLOGY

6.1.MATERIALS USED

A.List of Materials used in the formulation

Table.No:5.List of Materials used in the formulation

1	ZANAMIVIR	Chandra labs, Hyderabad
2	HPMC	Sisco research laboratories Pvt.Ltd Mumbai
3	XANTHUM GUM	MYL CHEM Mumbai
4	GUAR GUM	MYL CHEM Mumbai
5	PVP	Sisco research laboratories Pvt.Ltd Mumbai
6	ETHYL CELLULOSE	MYL CHEM Mumbai
7	SODIUM BICARBONATE	SD Fine Chemicals Ltd., Mumbai
8	MICRO CRYSTALLINE CELLULOSE	SD Fine Chemicals Ltd., Mumbai
9	MAGNESIUM STEARATE	SD Fine Chemicals Ltd., Mumbai

B.EQUIPMENTS USED

Table.No:6.List of Equipment used for the formulation

S. No	Name of the Equipment	Manufactured by
1	Dissolution apparatus	Electro Lab
2	Tablet punching machine	Cad mach
3	U.V. Spectrophotometer	Analytical
4	Analytical Balance	Adair Dutt Instruments Pvt. Ltd., AD50B
5	Friability Apparatus	Electro Lab
6	Hardness tester	Ketan
7	FT-IR Spectrometer	Bruker

6.2. PREFORMULATION STUDIES

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Pre-formulation studies yield necessary knowledge to develop suitable formulation for toxicological use. It gives information needed to define the nature of the drug substance and provide a dosage form. Hence, the following pre-formulation studies were performed for the obtained sample of drug.

Description and Solubility

Zanamivir is a white crystalline powder. It was found to be Highly soluble in water.

6.3.STANDARD GRAPH OF ZANAMIVIR

A.Standard Stock solution: 100 mg of zanamivir was dissolved in 100 ml of 0.1N HCL (1000 µg/ml)

Calibration curve of Zanamivir in 0.1N HCL

From the above stock solution, 1 ml was transferred into a 10 ml volumetric flask and volume was adjusted to 10 ml that corresponded to 100 µg/ml zanamivir in solution. From that solution different aliquots of 1.6, 1.8, 2, 2.2 and 2.4 ml were transferred to 10ml volumetric flask, volume was adjusted with 0.1N HCL, which gave a concentration of 16,18,20,22 and 24 µg/ml of final standard. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 216 nm.

B.Drug-Excipients Compatiblity study:

Zanamivir was mixed with all excipients, used in the formulation in different ratios and subjected to Physical observation/FTIR.

Drug-Excipient Compatiblity study (FTIR):

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-400 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press.

6.4. EXPERMENTAL METHODS

FORMULATION AND PREPARATION OF ZANAMIVIR FLOATING TABLETS: All the formulations were prepared by direct compression method using different Polymers.

PROCEDURE:

1. Zanamivir and all other ingredients were individually passed through sieve ≠ 60.

2. All the ingredients were mixed thoroughly by triturating up to 15 min.

3. The powder mixture was lubricated with Magnesium stearate The tablets were prepared by using direct compression method according to the formulation table.

Table.No:7.Composition of different formulations

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Zanamivir	75	75	75	75	75	75
HPMC	105	122.5	140	--	--	--
Xanthum gum	--	--		105	--	--
Guar gum	--	--		--	105	--
Ethyl cellulose	--	--		--	--	105
PVP	17.5	17.5	17.5	17.5	17.5	17.5
Sodium bicarbonate	52.5	52.5	52.5	52.5	52.5	52.5
MCC	96.5	79	61.5	96.5	96.5	96.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5
Total weight	**350mg**	**350mg**	**350mg**	**350mg**	**350mg**	**350mg**

PVP – Poly vinyl pyrrolidine , HPMC- Hydroxy Propyl methyl cellulose,

MCC- Micro crystalline cellulose

6.5. EVALUATION OF PRE COMPRESSION PARAMETERS

A. Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved granules into a graduated cylinder via a large funnel and measure the volume and weight.

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

Bulk density was expressed in g/cc.

B. Tapped density:

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume of granules}}$$

C. Carr's Index (CI):

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{(TD-BD)\ x100}{TD}$$

Where TD = Tapped density

BD = Bulk density

Table.No:8.Flow properties and corresponding Carr's Index values

Excellent	<10
Good	11 – 15
Fair	16 – 20
Possible	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very very poor	>38

D.Hausner's Ratio:

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density / Bulk density

Table.No:9.Flow Properties and Corresponding Hausner's ratio

Excellent	1.00 – 1.11
Good	1.1 – 1.18
Fair	1.19 – 1.25
Possible	1.26 -1.34
Very poor	1.35 -1.45
Very very poor	>1.60

E.Angle of repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal.

$$\mathbf{Tan\theta = h/r}$$

Where, h= height of the heap

r= Radius of the heap

Table.No:10. Flow Properties and Corresponding Angle of Repose

ANGLE OF REPOSE	POWDER FLOW
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

6.6.EVALUATION OF TABLETS[38]:

The formulated tablets were evaluated for the following physicochemical characteristics:

A.General appearance:

The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture and odor.

B.Hardness:

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

C.Weight Variation:

Fig.No:12.Weight Variation Apparatus

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible

limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

D.Friability test:

20 previously weighed tablets were placed in the friability apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,

Percentage friability = initial weight-final weight /initial weight × 100.

Fig.No:13.Friability Apparatus

E.Drug content:

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Zanamivir was transferred in to a 100 ml volumetric flask and the volume adjusted to 100ml with 0.1N HCl. Further 1ml of the above solution was diluted to 100 ml with 0.1N HCl and check the absorbance of the resulting solution was observed at 216nm.

F.*In-vitro* Buoyancy studies:

The *in-vitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).

G.Swelling Index Studies:

The swelling behavior of a dosage unit wasmeasured by studying its weight gain. The swelling indexof tablets was determined by placing the tablets in thebasket of dissolution apparatus using dissolution mediumas 0.1N HCl at 37±0.5°C. After 1, 4 and 6h each dissolution basket containing tablet waswithdrawn, blotted with tissue paper to remove theexcess water and weighed on the analytical balance(Schimdzu,

AX 120). The experiment was performedin triplicate for each time point. Swelling index wascalculated by using the following formula

$$\text{Swelling index} = \frac{\text{(Wet weight of tablet – Dry weight of tablet)}}{\text{Dry weight of tablet.}}$$

H. *In-Vitro* Dissolution Studies of Tablets:

Dissolution parameters:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,8 and 10
Temperature	--	37 $\pm$ 0.5°C

Dissolution Study[40]:

900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 $\pm$ 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 10 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 216 nm.

Fig.No:14.Dissolution Apparatus

Release Kinetics :

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, diffusion and Peppa's-Korsemeyer equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's- Korsemeyer equation. The results are given in Table .

Zero Order Release Kinetics:

It defines a linear relationship between the fractions of drug released versus time.

$$Q = k_o t$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$In\ (1-Q) = - K_1 t$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q=K_2t^{½}$$

Where, K2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

Koresmeyer Peppas

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power Law).

$$M_t/M_\alpha = K.t^n$$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the $M_t/M_\alpha$is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table. A plot between log of M_t/M_α against log of time will be linear if the release obeys Peppa's and Korsemeyer equation and the slope of this plot represents "n" value.

Table.No:11.Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion Exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

6.7.Stability studies

Stability studies were carried out according to ICH guidelines by exposing the. Formulations f5 in their final packing mode to the temperature 40±2°C and relative humidity 75±5 % in programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Aliquot were withdrawn at 30 and 60 days and analyzed for change in drug content and *in-vitro* dissolution profile

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing:

1. 21˚C/45% RH analyzed every month for period of three months.

2. 25˚C/60% RH analyzed every month for period of three months.

3. 30˚C/70% RH analyzed every month for period of three months.

Fig.No:15.Stability Chamber

7. RESULTS AND DISCUSSION

7.1.STANDARD GRAPH OF ZANAMIVIR:

Table.No:12. Standard graph of ZANAMIVIR

Conc (µg/ml)	Absorbance
16	0.421
18	0.472
20	0.520
22	0.562
24	0.612

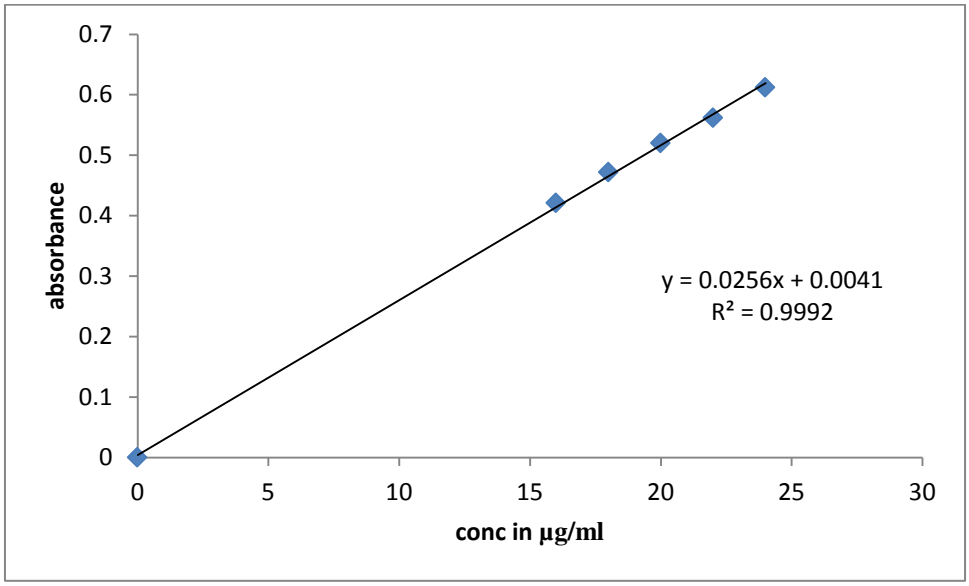


Fig.No:16.Standard calibration curve of Zanamivir

7.2.FT-IR STUDIES:

The FTIR spectra of the drug (alone), polymer (alone) and the drug-polymer (mixture) were recorded by the potassium bromide pellet method. From the infrared spectra it is clearly evident that there were no drug-polymer interactions of the drug.

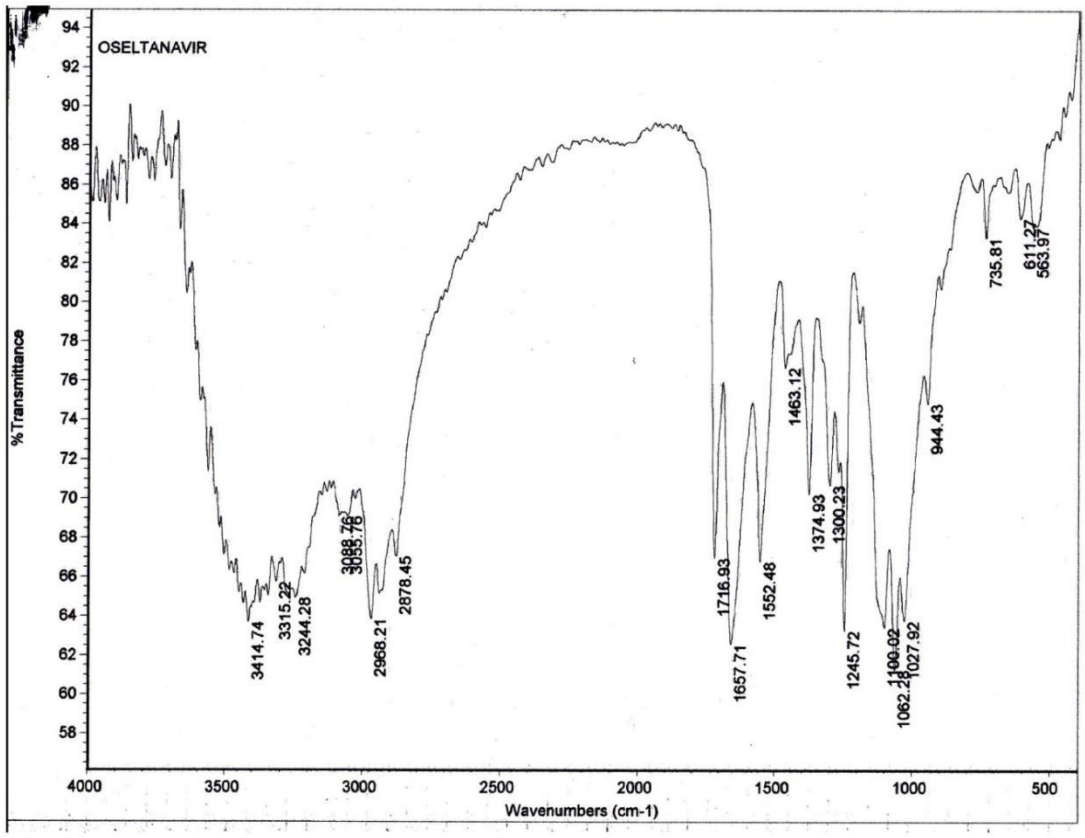


Fig.No:17. FT-IR Spectra of Zanamivir

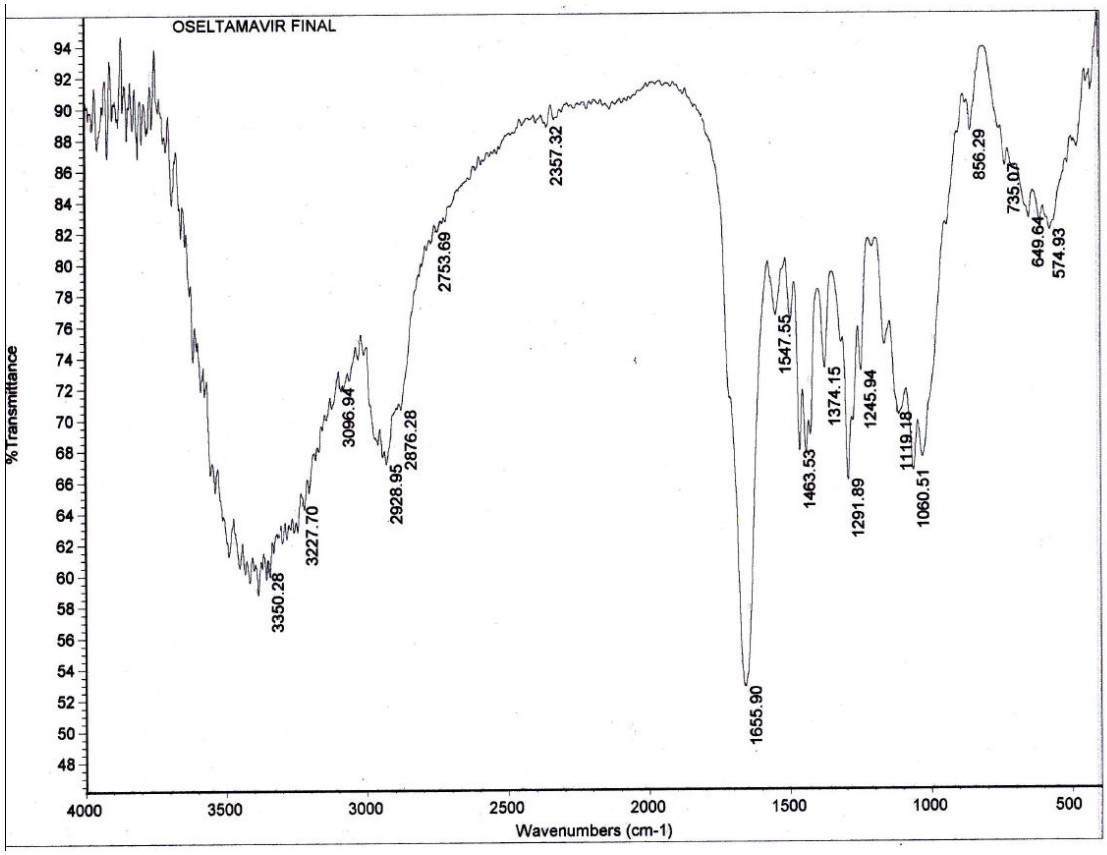


Fig.No:18.FT-IR Spectra of Zanamivir final formulation

7.3. PREFORMULATION STUDIES OF POWDERED BLEND

Preformulation studies of powdered blend parameters like bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose as shown in the table below.

Table.No:13.Pre-compression parameters for formulation batches

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.721±0.045	0.87± 0.01	17.126±0.6	1.206±0.06	26.62±0.21
F2	0.710±0.043	0.873±0.04	19.714±0.7	1.251±0.04	27.46±0.11
F3	0.41±0.045	0.483±0.5	15.113±0.8	1.178±0.08	28.32±0.31
F4	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06±0.31
F5	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58±0.15
F6	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44±0.11

(n = 3)

POST COMPRESSION PARAMETERS

The results of the weight variation, hardness, friability, drug content, Buoyancy lag time and Total floating time of the Tablets are given in table

In-vitro Buoyancy studies:

In-vitro buoyancy of the tablets from each formulation (F1 to F6) was evaluated and the results are mentioned in Table 14. Where, the highest and lowest floating lag time (FLT) was observed with the formulation F1 and F6 respectively. The concentration of the natural polymers increases the floating lag time also increases and total floating time observed for all the formulations was >10 hours.

At initial time

After 20 Sec

After 10 hrs

Table.No:14.Post compression evaluation parameters of ZANAMIVIR floating Tablets

Formulation No.	Avg. Weight (Mean± S.D) (n=20)	Hardness (kg/cm^2) (n=3)	Friability (Mean±S.D) (n=6)	% Drug content (mg)	Buoyancy Lag time (min)	Total floating Time(hrs)
F1	353±0.6	7.2±0.4	0.546	98±0.7	26	5
F2	350±0.9	7.5±0.4	0.612	99±0.5	18	6
F3	347±0.3	7.4±0.6	0.527	98±0.6	20	10
F4	351±0.4	7.6±0.1	0.511	99±0.6	30	8
F5	346±0.8	7.6±0.6	0.525	99±0.6	61	8
F6	354±0.8	7.3±0.4	0.555	98±0.5	35	10

7.4. Swelling index studies

Table.No:15.Swelling index studies of ZANAMIVIR floating Tablets

Time(hr)	Swelling index ratio (%)					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
2	32	35	42	46	50	55
4	46	48	50	51	58	60
6	52	55	58	65	67	72
8	49	50	52	54	59	64

7.5. Dissolution studies

Table.No:16.Dissolution Data Of ZANAMIVIR Floating Tablets

TIME (hr)	% of Drug Release					
	F1	F2	F3	F4	F5	F6
1	18.8	14.3	11.3	16.5	12.4	9.2
2	39.9	22.2	21.4	29.8	30.8	19.3
3	52.3	37.6	32.8	41.9	42.3	26.9
4	76.9	46.8	46.1	50.2	49.4	38.2
5	92.8	76.8	58.4	61.1	60.3	46.8
6	92.8	96.3	69.5	72.7	76.4	58.3
8	92.8	96.3	79.9	96.3	90.2	71.4
10	92.8	96.3	90.4	96.3	97.4	84.9

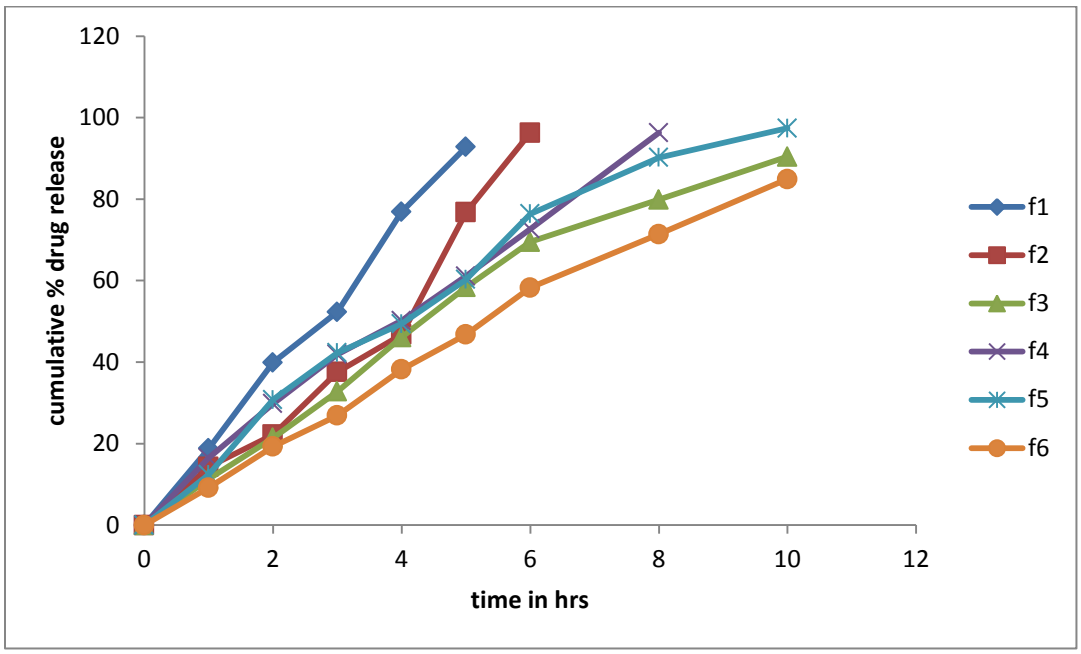


Fig.No:19.Dissolution profile of Zanamivir Floating Tablets

The % Cumulative drug release of all the formulations F1, F2, F4 was not able to sustain the drug release for 10 hrs. F3 and F6 formulations showed good integrity for 10 hrs. F4 formulation was optimised based on the floating behaviour. The optimized formulation F5 showed % drug release of 97.4% for 10 hrs which shows greater release compare to all other formulation.

Fig 20 : Dissolution profile of Zanamivir Floating Tablets of F1

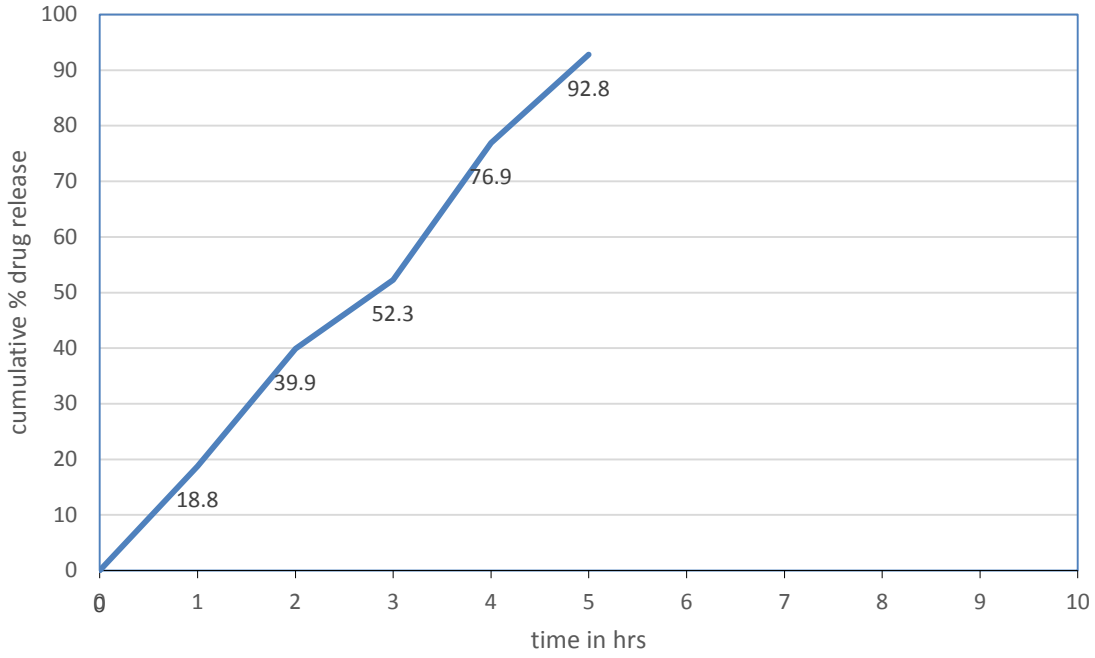


Fig 21 : Dissolution profile of Zanamivir Floating Tablets of F2

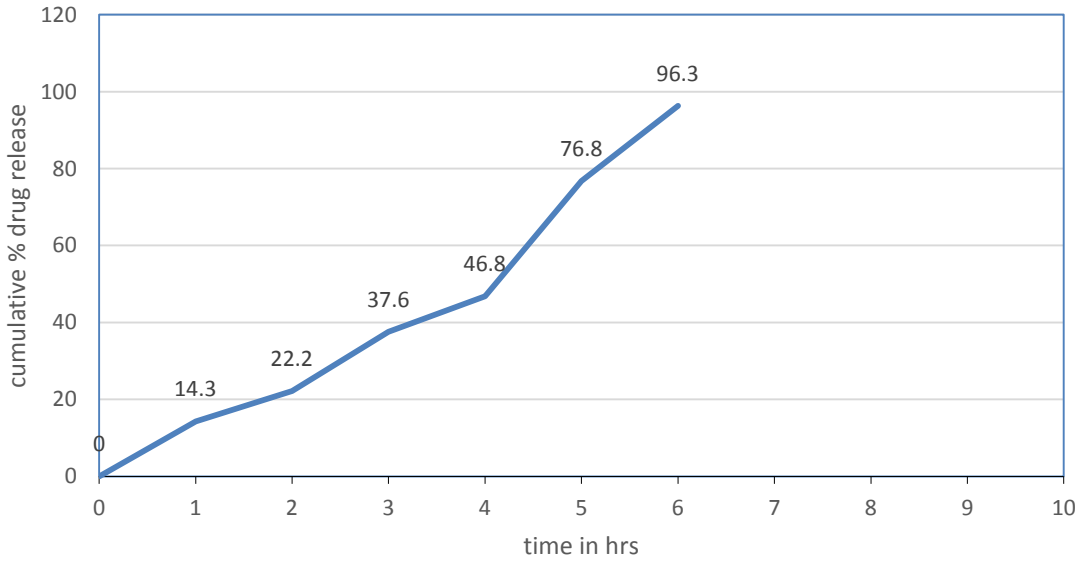


Fig 22 : Dissolution profile of Zanamivir Floating Tablets of F3

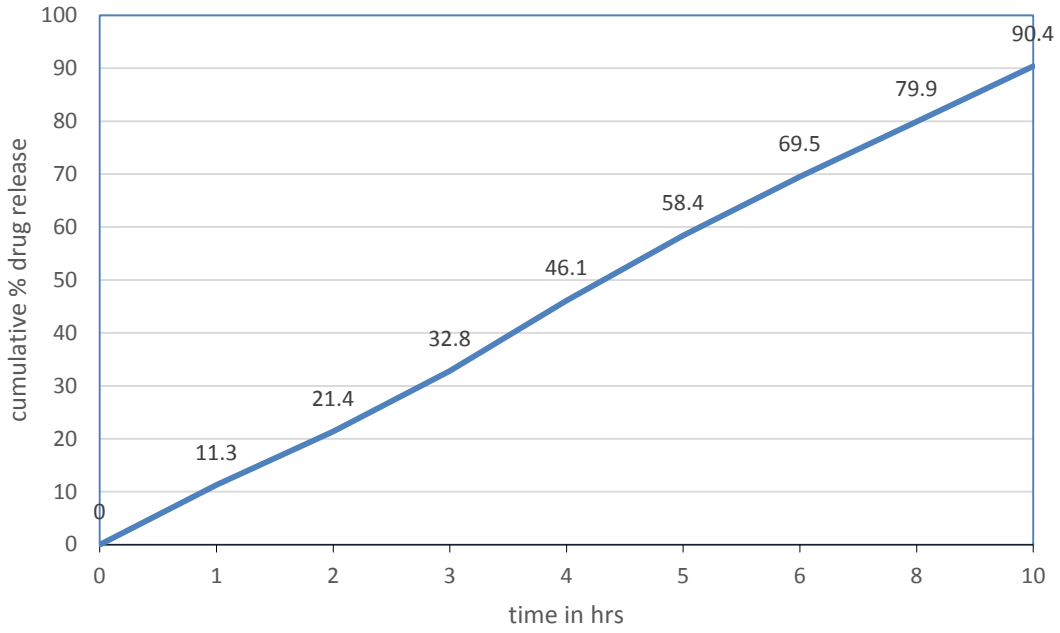


Fig 23 : Dissolution profile of Zanamivir Floating Tablets of F4

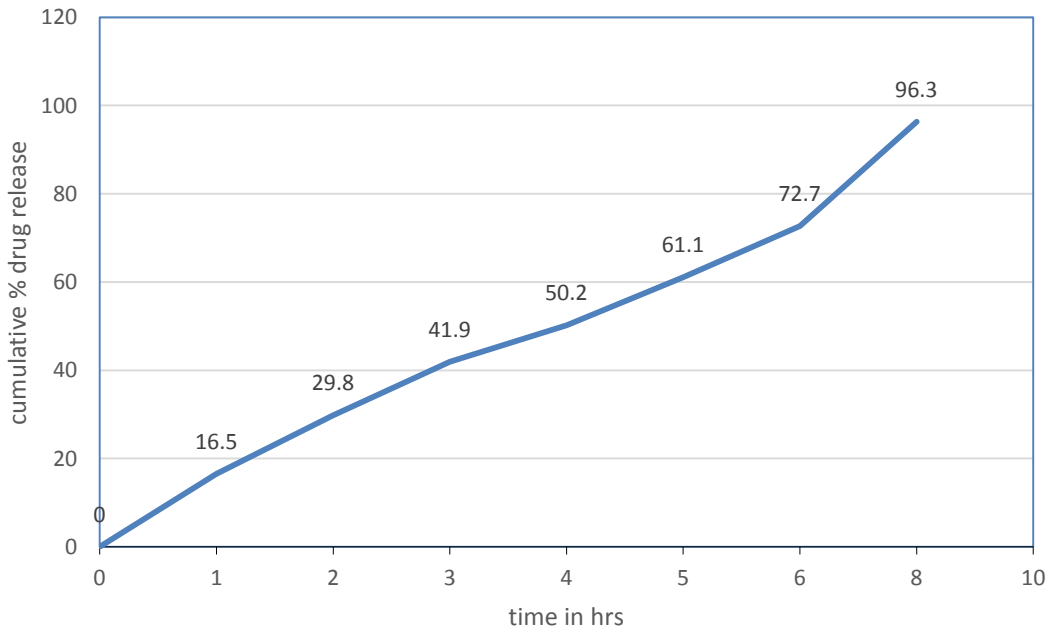


Fig 24 : Dissolution profile of Zanamivir Floating Tablets of F5

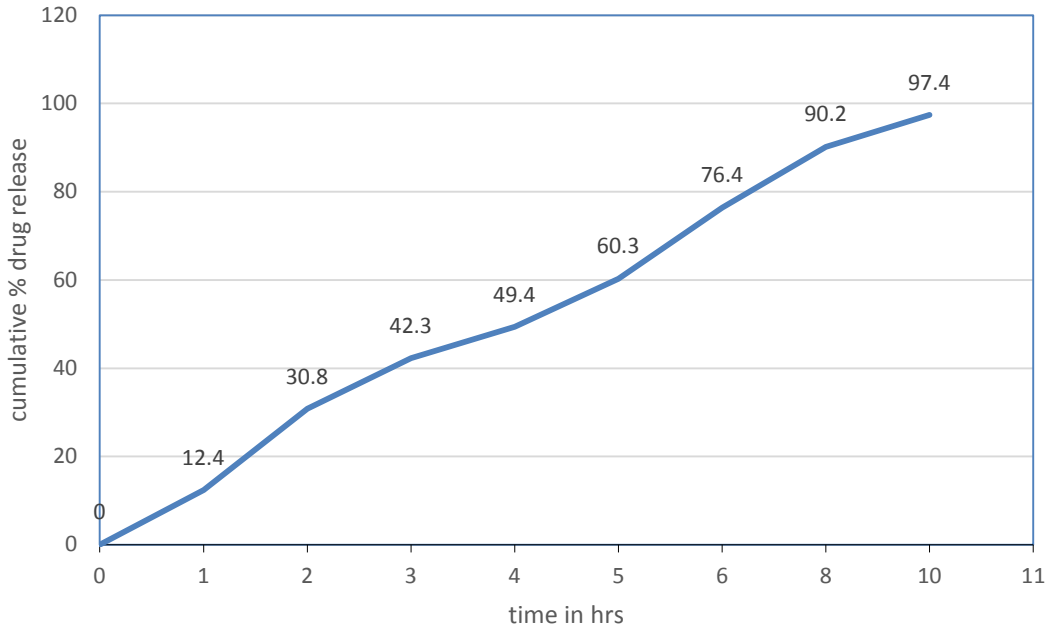
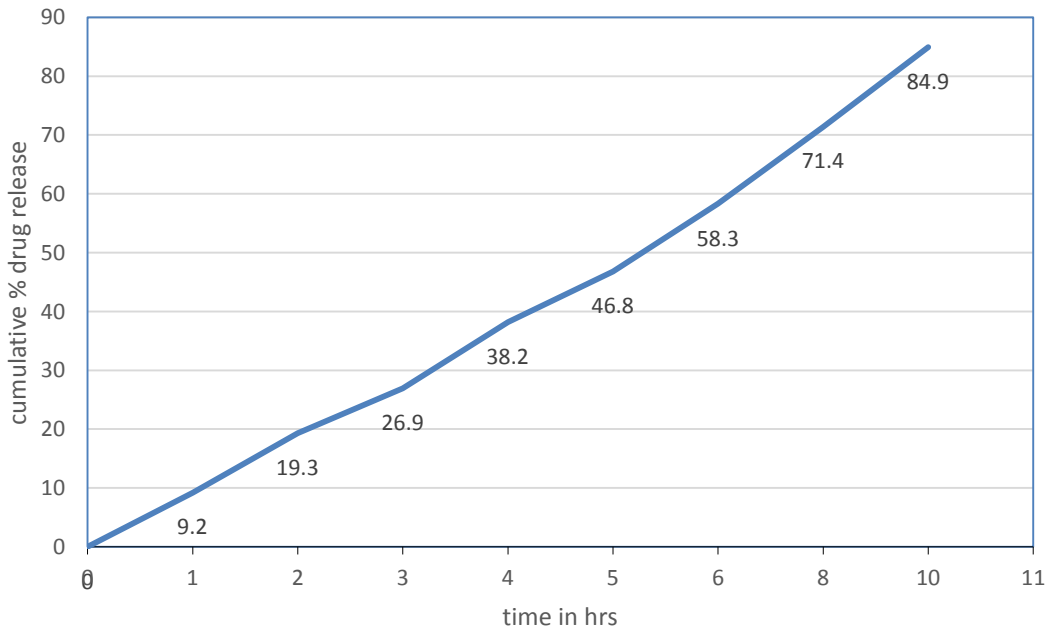


Fig 25 : Dissolution profile of Zanamivir Floating Tablets of F6



7.6.KINETIC MODELLING AND MECHANISM OF DRUG RELEASE:

The results of kinetic equations applied to dissolution profiles of optimized batch F5 were determined as follows.

Table.No:17. Kinetic values obtained from different plots of F5 formulation

	ZERO ORDER	FIRST ORDER	HIGUCHI ORDER	PEPPAS ORDER
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	10.0480	-0.1512	33.7231	1.4567
Intercept	7.4806	2.1695	-12.0120	0.7304
Correlation	0.9823	-0.9609	0.9772	0.8513
R 2	0.9649	0.9235	0.9549	0.7247

The release kinetics of all the dosage forms were calculated using zero-order, first-order, higuchi and krosemeyer-peppas. Optimized formulation was found to follow higuchi release kinetics. The optimized formulation F5 was found to exhibit zero–order which shows that the diffusion along with dissolution of the drug from the tablet.

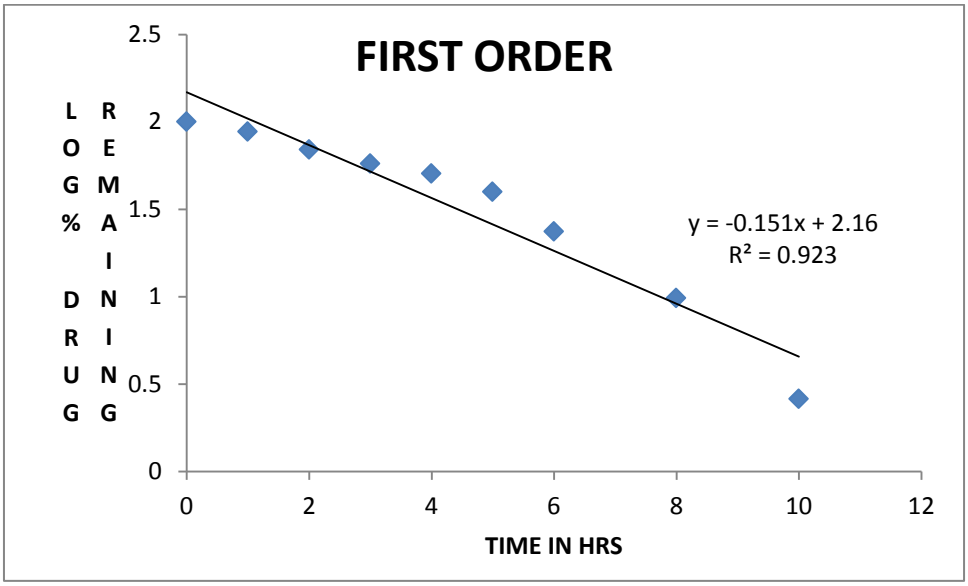


Fig.No:26. First order release model for F5 formulation

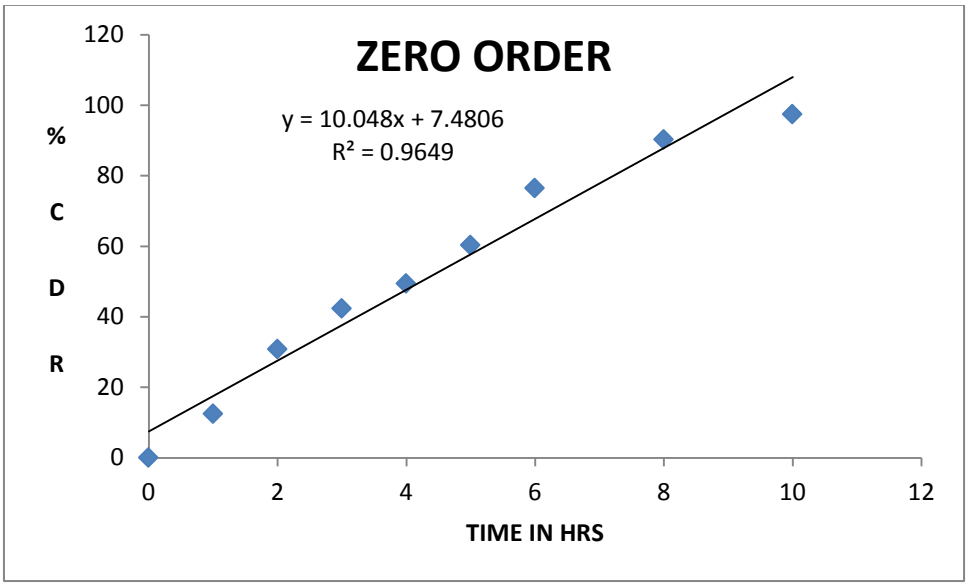


Fig.No:27. Zero order release model for F5 formulation

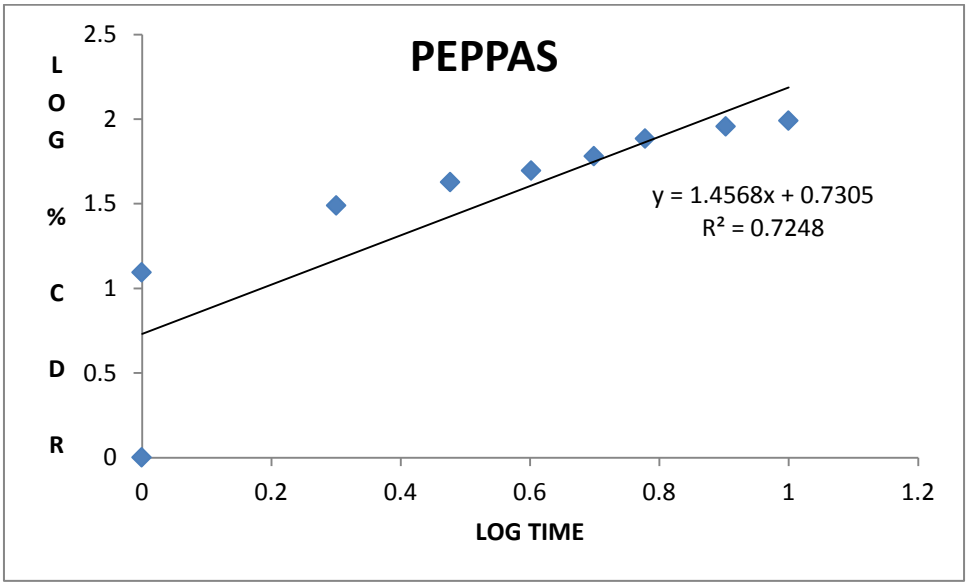


Fig.No:28. Peppas release model for F5 formulation

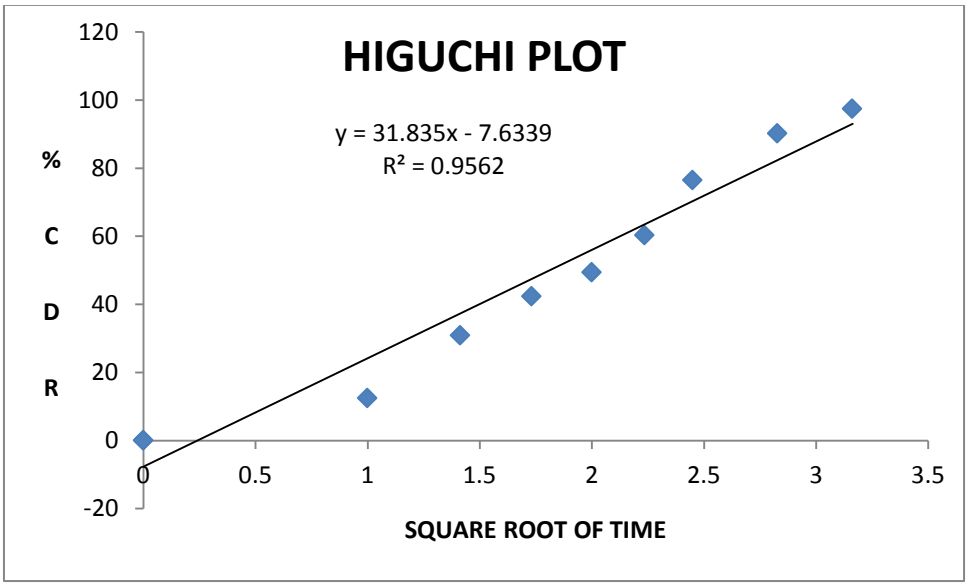


Fig.No:29. Higuchi release model for F5 formulation

7.7. ZANAMIVIR FLOATING TABLETS

Table.No:18.Stability data of optimised formulation F5

S. No	Time points (hr)	Initial	Cumulative % Drug Release			
			25˚C/60%RH		40˚C/75%RH	
			1st Month	3rd Month	1stMonth	3rdMonth
1	1	12.4	12.2	11.7	11.2	10.7
2	2	30.8	30.4	30.1	29.4	29.1
3	3	42.3	42.1	41.8	39.6	39.2
4	4	49.4	49.0	48.6	47.8	47.4
5	5	60.3	58.3	59.4	59.1	58.6
6	6	76.4	76.1	75.5	75.1	74.9
7	8	90.2	89.8	89.2	88.7	88.1
8	10	97.4	97.1	96.5	96.1	95.8
9	Assay	99.5	99.2	99.1	98.7	98.5

(mean ± SD) (n=3)

The optimized formula was kept for stability studies. The cumulative % Drug release kinetics was used to predict the stability of the preparation. The mean values of these parameters were compared with that obtained on 1st month as described in table. The results are shown in Table.No.18. There was less significant change in % entrapment efficiency at storage temperatures after 3 month of production which indicates the stability of preparation.

8. SUMMARY AND CONCLUSION

- Gastro retentive dosage form using Guar gum was prepared to develop a floating tablet of Zanamivir that could retain in the stomach for longer periods of time delivering the drug to the site of action, i.e., stomach.

- The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture.

- The post-compression parameters of all formulations were determined and the values were found to be satisfactory.

- From the drug content and *in-vitro* dissolution studies of the formulations, it was concluded that the formulation F5 i.e. the formulation containing Guargum, PVP, Sodium bicarbonate, micro crystalline cellulose and Magnesium stearate is the best formulation.

- The % Cumulative drug release of all the formulations F1, F2, F4 was not able to sustain the drug release for 10 hrs. F3 and F6 formulations showed good integrity for 10 hrs. F4 formulation was optimised based on the floating behaviour. The optimized formulation F5 showed a %drug release of 97.4% for 10 hrs which shows greater release compare to all other formulation.

As a result of this study it may be concluded that the floating tablets using a guar gum in optimized concentration can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a controlled manner. The concept of formulating floating tablets of Zanamivir offers a suitable and practical approach in serving desired objectives of gastro retentive floating tablets.

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